

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>C25D 9/08, A61L 27/00</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 98/13539</b> <b>(43) International Publication Date:</b> 2 April 1998 (02.04.98)
<b>(21) International Application Number:</b> PCT/GB97/02527 <b>(22) International Filing Date:</b> 16 September 1997 (16.09.97) <b>(30) Priority Data:</b> 8/252012                      24 September 1996 (24.09.96)    JP <b>(71) Applicants (for all designated States except US):</b> ABONETICS LIMITED [GB/GB]; IRC in Biomedical Materials, Queen Mary & Westfield College, Mile End Road, London E1 4NS (GB); MITSUBISHI MATERIALS CORPORATION [JP/JP]; 5-1, Otemachi 1-chome, Chiyoda-ku, Tokyo 100 (JP). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> BONFIELD, William [GB/GB]; 48 Harmer Green Lane, Digswell, Welwyn, Herts AL6 0AT (GB). BEST, Serena, Michelle [GB/GB]; The Old Manse, 17 High Street, Ridgmont, Bedfordshire MK43 0TS (GB). ASAKA, Nobuyuki [JP/JP]; 303 Daini-Kato Heights, 1-155, Amanuma-cho, Omiya-shi, Saitama 330 (JP). <b>(74) Agent:</b> BOULT WADE TENNANT; 27 Fumival Street, London EC4A 1PQ (GB).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> METHOD FOR COATING A CALCIUM PHOSPHATE COMPOUND ONTO A METALLIC MATERIAL <b>(57) Abstract</b> <p>A method for coating a calcium phosphate compound onto a metallic material, which method comprises electrodepositing the calcium phosphate compound from an aqueous solution containing calcium ions, phosphate ions and a complex forming agent onto an electrode comprising the metallic material. The coating layer obtained by this process comprises fine and uniform particles of a calcium phosphate compound and has a high bond strength.</p>		

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MR	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MT	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	JP	Japan	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	KE	Kenya	NL	Netherlands	VN	Viet Nam
CG	Congo	KG	Kyrgyzstan	NO	Norway	YU	Yugoslavia
CH	Switzerland	KP	Democratic People's Republic of Korea	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KR	Republic of Korea	PL	Poland		
CM	Cameroon	KZ	Kazakhstan	PT	Portugal		
CN	China	LC	Saint Lucia	RO	Romania		
CU	Cuba	LI	Liechtenstein	RU	Russian Federation		
CZ	Czech Republic	LK	Sri Lanka	SD	Sudan		
DE	Germany	LR	Liberia	SE	Sweden		
DK	Denmark			SG	Singapore		
EE	Estonia						

**METHOD FOR COATING A CALCIUM PHOSPHATE COMPOUND  
ONTO A METALLIC MATERIAL**

5 The present invention relates to a method for coating a calcium phosphate compound onto a medical implant metallic material such as an artificial articulation, an artificial bone, or an artificial root of a tooth.

10 As an implant material used as a substitute for a hard tissue of an organism lost by disease or by accident, titanium, titanium alloys, cobalt-chromium alloys, stainless steel and the like have hitherto been employed. However, these metallic materials do not  
15 bind directly to the tissue of the organism, thus raising problems of low initial bonding strength, and loosening over longer periods of time.

As a method for improving the initial bonding strength of the implant material, a method has been developed in which a bone cement including poly methyl  
20 methacrylate (PMMA) is injected into a site to be treated and solidified. However, in this method, there is a problem that the heat generated by the solidifying reaction affects the surrounding tissue.

In order to solve these problems, a method has  
25 been proposed utilizing a metal implant material on which a calcium phosphate compound such as hydroxyapatite is coated on its surface. In this method, by connecting the implant material directly with hard tissue such as bone via a bioactive coating  
30 layer, the initial bond strength and stability for a prolonged time may be improved.

As methods for forming such a coating layer, plasma spraying, sputtering, dip coating and sol-gel coating methods have hitherto been employed. Of these,  
35 the plasma spraying method is a relatively practical method, but has problems such as the formation of

soluble by-products or amorphous components, which results in the dissolution of the coating layer after implantation, and ablation at a gap between a substrate and the coating layer. The methods for forming the  
5 coating layer other than the plasma spraying method also encounter problems such as an insufficient bonding strength and nonuniformity of the coating layer, and therefore are not sufficiently practical.

We have now developed a method for coating a  
10 calcium phosphate compound by which a coating layer composed of fine and uniform particles of a calcium phosphate compound and having a high bond strength is readily formed.

According to the present invention, there is  
15 provided a method for coating a calcium phosphate compound onto a metallic material, which method comprises electrodepositing the calcium phosphate compound from an aqueous solution containing calcium ions, phosphate ions and a complex forming agent onto  
20 an electrode comprising the metallic material.

In a particular aspect the present invention provides a method as described above wherein the calcium phosphate compound is hydroxyapatite, and the pH of the aqueous solution is controlled to be not less  
25 than 4.0 for the electrodepositing.

In a further aspect the present invention provides a method wherein the calcium phosphate compound salt is other than hydroxyapatite, and the method further comprises the step of immersing the material having the  
30 calcium phosphate compound electrodeposited thereon in an aqueous solution having pH of not less than 4.0, whereby the calcium phosphate compound salt is converted to hydroxyapatite.

In the coating method of the present invention, a  
35 calcium phosphate compound salt is electrodeposited

onto a metallic material from an aqueous solution containing calcium ions, phosphate ions and a complex forming agent.

5 The material to be coated is not limited as long as it is made of metal and does not spoil the effect of the present invention. Metals which are superior in anti-corrosive properties and do not exhibit toxicity in having organisms, such as titanium, a titanium alloy, stainless steel or a cobalt-chromium alloy may  
10 be employed.

As the configuration of the material to be coated, any configurations may be employed including a plate, a sphere, a cylinder, a prism, a circular cone, a pyramid, and a variety of other forms imitating a  
15 tooth or a bone.

The aqueous solution containing calcium ions, phosphate ions and a complex forming agent may be prepared by dissolving in water a compound containing calcium ions, a compound containing phosphate ions, and  
20 a complex forming agent.

The compound containing calcium ions may include, e.g.  $\text{Ca}(\text{OH})_2$ ,  $\text{Ca}(\text{NO}_3)_2$ ,  $\text{CaC}_2$ ,  $\text{Ca}(\text{CH}_3\text{COO})_2$ , calcium citrate or calcium lactate. The compound containing phosphate ions may include, e.g.  $\text{H}_3\text{PO}_4$ ,  $\text{Na}_3\text{PO}_4$ ,  $(\text{NH}_4)_3\text{PO}_4$ ,  
25  $\text{K}_3\text{PO}_4$ , or a salt in which a part of the cation in these salts is substituted by hydrogen (e.g.  $(\text{NH}_4)_2\text{HPO}_4$ ). Instead of employing both a compound containing calcium ions and a compound containing phosphate ions, a compound containing both phosphate ions and calcium  
30 ions, such as hydroxyapatite, calcium tertiary phosphate, calcium quaternary phosphate or calcium hydrogen phosphate, may be employed.

As to the concentration of the calcium ions and the phosphate ions in the above aqueous solution, the  
35 concentration of  $[\text{Ca}^{2+}]$  is preferably 0.01 to 2.0 mol/l,

and the concentration of  $[\text{PO}_4^{3-}]$  is preferably 0.005 to 2.0 mol/l. As to the ratio of calcium ions and phosphate ions in the aqueous solution, the Ca/P molar ratio is preferably 1.0 to 3.0. By suitably regulating these ion concentrations, the thickness of the coating layer may be controlled.

The complex forming agent may include citric acid, ethylenediaminetetraacetic acid (EDTA), lactic acid or nitrilotriacetic acid (NTA). The preferable concentration of the complex forming agent in the aqueous solution is 0.01 to 1.0 mol/l.

In the method of the present invention, a calcium phosphate compound salt is electrodeposited on the metallic material to be coated as an electrode. For the electrodeposition, the counter electrode is not limited as long as it does not reduce the effect of the present invention, and may include the same metals as the material to be coated, and electrically conductive plastic materials. The distance between the electrodes in the aqueous solution is preferably 1 to 50mm.

The voltage for the electrodeposition is preferably 1 to 100V/cm<sup>2</sup>. By suitably regulating the voltage, the film forming rate and construction of the coating layer may be controlled.

The duration of the electrodeposition is preferably from 3 to 120 minutes. By suitably adjusting the duration of the electrodeposition, the thickness of the coating layer may be controlled.

Upon the electrodeposition, the temperature of the aqueous solution is preferably maintained at a constant temperature within a range of from 15° to 100°C. By maintaining the aqueous solution at a higher temperature, the time for the electrodeposition may be shortened. Also, if the aqueous solution is maintained at a higher temperature, a coating layer having a

larger particle size may be obtained, while if it is maintained at a lower temperature, a coating layer having a smaller particle size may be obtained.

5       Upon the electrodeposition, by regulating the aqueous solution at a pH of not less than 4.0, preferably 4.0 to 12.0, hydroxyapatite may be electrodeposited as the coating layer.

10       The aqueous solution may be regulated at a pH of not less than 4.0 by adding a pH regulating agent to the aqueous solution. It is not required to dissolve all of the pH regulating agent before beginning the electrodeposition. The agent may be added little by little after beginning the electrodeposition. That is, if the pH of the aqueous solution is not less than 4.0  
15       when the calcium ions, phosphate ions and the complex forming agent are dissolved therein, the pH regulating agent is not required to be added before beginning the electro-deposition, and may be added little by little after beginning the electrodeposition in order to  
20       prevent the pH value dropping below 4.0 during the electrodeposition, so that hydroxyapatite may be electrodeposited.

25       As the pH regulating agent, ammonia, sodium hydroxide or potassium hydroxide may be employed. In terms of preventing contamination by undesired metal ions, ammonia is particularly preferred. In the case of adding the pH regulating agent little by little during the electrodeposition, the pH regulating agent is preferably prepared as an alkaline solution by  
30       dissolving the agent in water. The preferred concentration of the alkaline solution is, for example, in the case of employing ammonia, 0.03 to 0.5 mol/l, and in the case of employing sodium hydroxide, 0.01 to 0.1 mol/l.

The calcium phosphate compound in the coating layer obtained by the coating method of the present invention may include calcium hydrogen phosphate dihydrate ( $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$ ), monetite ( $\text{CaHPO}_4$ ), calcium  
5 tertiary phosphate ( $\text{Ca}_3(\text{PO}_4)_2$ ), or the aforementioned hydroxyapatite.

If a layer of a calcium phosphate compound salt other than hydroxyapatite is obtained by the electrodeposition, the layer of the calcium phosphate  
10 compound other than hydroxyapatite obtained by the electrodeposition may be converted into the more stable hydroxyapatite by immersing the coated material having the calcium phosphate compound salt electrodeposited thereon in an aqueous solution having pH of not less  
15 than 4.0, preferably 4.0 to 12.0. The step may be performed by, but is not limited to, adjusting the pH of the aforementioned aqueous solution employed upon the electrodeposition to the desired pH value by, e.g. adding alkali while the coated material is kept  
20 immersed in the aqueous solution, or by transferring and immersing the coated material into another aqueous solution, the pH of which has been adjusted to the desired pH value by, e.g. adding alkali after the electrodeposition. The preferred duration of the  
25 immersion is from 10 to 50 hours. As the alkali, ammonia, sodium hydroxide or potassium hydroxide may be employed. In terms of preventing contamination by undesirable metal ions, ammonia is particularly preferred.

30 The coating layer of the calcium phosphate compound obtained by the method of the present invention may further be subjected to a heat treatment for improving bonding strength. Even the heat treatment at relatively low temperature at which the coated  
35 material is not damaged, e.g. about  $750^\circ\text{C}$  in the case of



titan, can improve the bonding strength of the coating layer. It is believed that the bonding strength of the coating layer can be improved at such a relatively low temperature since the aqueous solution as a coating bath has an electrophoresis effect so that the coating layer is formed of finer particles on the material to be coated as the electrode, than that of a conventional layer.

With the method for coating of the present invention, a coating layer of a calcium phosphate compound is formed by electrodeposition, and thus a calcium phosphate compound composed of fine and uniform particles may be coated even on the surface of a metal material having a complicated configuration. Therefore, the present invention is useful as a method for improving the biological compatibility of implant materials.

The present invention is described in more in detail with reference to Examples herein below, but the present invention is not limited thereto. In the following Examples, all of the reagents used are manufactured by BDH.

#### EXAMPLE 1

0.1 mol of calcium hydroxide, 0.06 mol of orthophosphoric acid and 0.2 mol of citric acid were dissolved in 1 litre of distilled water. This aqueous solution was poured into three vessels in water baths, and controlled at temperatures of 20°C, 60°C and 90°C, respectively. In each of the vessels, two pure titanium plates (50 x 20 x 1 mm) were inserted at an electrode separation of 10 mm, and electrodeposition was performed at DC 20V for 30 minutes. As a result, porous coating layers of calcium hydrogenphosphate

-8-

dihydrate ( $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$ ) having thicknesses of  $5\mu\text{m}$ ,  $10\mu\text{m}$  and  $20\mu\text{m}$ , respectively, were obtained on the surface of each cathode.

5

**EXAMPLE 2**

0.1 mol of calcium nitrate, 0.06 mol of ammonium phosphate and 0.1 mol of EDTA were dissolved in 1 litre of distilled water. This aqueous solution was poured  
10 into a vessel in a water bath, and controlled at a temperature of  $95^\circ\text{C}$ . In the vessel, a pure platinum plate (anode,  $50 \times 20 \times 0.1$  mm) and a stainless-steel SUS316L plate (cathode,  $50 \times 20 \times 1$  mm) were inserted at an electrode separation of 10 mm, and  
15 electrodeposition was performed at DC 10V for 30 minutes. As a result, a coating layer of monetite ( $\text{CaHPO}_4$ ) having a thickness of  $10\mu\text{m}$  was obtained on the surface of the cathode.

20

**EXAMPLE 3**

0.2 mol of calcium hydroxide, 0.12 mol of orthophosphoric acid and 0.5 mol of lactic acid were dissolved in 1 litre of distilled water. This aqueous  
25 solution was poured into three vessels in water baths, and controlled at temperatures of  $20^\circ\text{C}$ ,  $60^\circ\text{C}$  and  $90^\circ\text{C}$ , respectively. In each of the vessels, two plates ( $50 \times 20 \times 1$  mm) of a titanium alloy containing 6wt% of aluminum and 4wt% of vanadium (referred to hereinafter  
30 as Ti-6Al-4V alloy) were inserted at an electrode separation of 10 mm, and electrodeposition was performed at DC 10V for 20 minutes. As a result, a dense coating layer of monetite having thicknesses of  $10\mu\text{m}$ ,  $15\mu\text{m}$  and  $30\mu\text{m}$ , respectively, were obtained on the  
35 surface of each cathode.

**EXAMPLE 4**

0.1 mol of calcium hydroxide, 0.06 mol of orthophosphoric acid and 0.3 mol of lactic acid were dissolved in 1 litre of distilled water. This aqueous solution was poured into a vessel in a water bath, and controlled at a temperature of 20°C. In the vessel, two pure titanium plates (50 x 20 x 1 mm) were then inserted at an electrode separation of 10 mm, and electrodeposition was performed at DC 5V for 10 minutes. As a result, a dense coating layer of calcium hydrogenphosphate dihydrate having a thickness of 30µm was obtained on the surface of the cathode.

After finishing the electrodeposition, ammonia was further added to the aqueous solution to adjust the pH to 5.0, and the cathode was immersed therein for 24 hours. As a result, the coating layer of calcium hydrogenphosphate dihydrate was converted into a uniform hydroxyapatite coating layer.

**EXAMPLE 5**

The coated alloy plate obtained in Example 3 with a 30µm thick coating layer was subjected to a heat treatment at 750°C for 60 minutes. Bonding strengths before and after the heat treatment were measured according to JIS H8666 "ceramic spraying test method" for comparison. As a result, the bonding strength was improved from 13MPa to 22MPa while the alloy plate, i.e. the coated material, was not damaged.

**COMPARATIVE EXAMPLE 1**

On a Ti-6Al-4V alloy plate which is the same as that of Example 3, monetite was sprayed by a plasma

-10-

spray gun manufactured by METCO Co. under the trade name of METCO 9MB to give a film thickness of  $30\mu\text{m}$ . The spraying was carried out under the conditions of 500A, 40V, at a spraying distance of 50mm, using a  
5 mixed gas of  $\text{Ar:H}_2$  of 100:3.

The bonding strength of the layer measured by the same method as Example 5 was 5MPa.

#### EXAMPLE 6

10

0.1 mol of calcium hydroxide, 0.06 mol of orthophosphoric acid and 0.2 mol of lactic acid were dissolved in 1 litre of distilled water. This aqueous solution was poured into three vessels in water baths,  
15 and controlled at the temperatures of  $20^\circ\text{C}$ ,  $60^\circ\text{C}$  and  $90^\circ\text{C}$ , respectively. In each of the vessels, two pure titanium plates ( $50 \times 20 \times 1$  mm) were inserted with the distance of 10 mm. An aqueous solution containing 0.1mol/l of ammonia was added dropwise into the vessels  
20 until the pH of the solution reached 4.5. Electrodeposition was then performed at DC 5V for 10 minutes while the aqueous ammonia solution was added dropwise using a low-speed motor with monitoring of the pH to be maintained at 4.5. As a result, dense coating  
25 layers of hydroxyapatite having thicknesses of  $5\mu\text{m}$ ,  $20\mu\text{m}$  and  $30\mu\text{m}$ , respectively, were obtained on the surface of each cathode. During the whole reaction, the pH was maintained at  $4.5 \pm 0.2$ .

30

#### EXAMPLE 7

0.1 mol of calcium nitrate, 0.06 mol of ammonium phosphate and 0.2 mol of citric acid were dissolved in 1 litre of distilled water. This aqueous solution was  
35 poured into two vessels in water baths, and controlled

at temperatures of 60°C and 90°C, respectively. In each of the vessels, two Ti-6Al-4V alloy plates (50 x 20 x 1 mm) were inserted at an electrode separation of 10 mm. 0.05mol/l of sodium hydroxide was added dropwise into the vessels until the pH of the solution reached 5.0. Electrodeposition was then performed at DC 10V for 20 minutes while sodium hydroxide was added dropwise using a low-speed motor with monitoring of the pH to be maintained at 5.0. As a result, coating layers of hydroxyapatite having thicknesses of 10µm and 25µm, respectively, were obtained on the surface of each cathode. During the whole reaction, pH was maintained at 5.0±0.2.

15

#### EXAMPLE 8

The coated alloy plate obtained in Example 7 with a 25µm coating layer was subjected to a heat treatment at 750°C for 60 minutes. Bonding strengths before and after the heat treatment were measured by the same method as in Example 5 and compared. As a result, the bonding strength was improved from 15MPa to 25MPa while the alloy plate, i.e. the coated material, was not damaged.

25

#### COMPARATIVE EXAMPLE 2

On the Ti-6Al-4V alloy plate which is the same as that of Example 7, hydroxyapatite was sprayed by a plasma spray gun manufactured by METCO Co. under the trade name of METCO 9MB to give a film thickness of 25µm. The spraying was carried out under the conditions of 500A, 40V, spraying distance of 50mm, using a mixed gas of Ar:H<sub>2</sub> of 100:3.

-12-

The bonding strength of the layer measured by the same method as in Example 5 was 6MPa.

**CLAIMS:**

1. A method for coating a calcium phosphate compound onto a metallic material, which method  
5 comprises electrodepositing the calcium phosphate compound from an aqueous solution containing calcium ions, phosphate ions and a complex forming agent onto an electrode comprising the metallic material.
- 10 2. A method as claimed in claim 1, wherein the calcium phosphate compound is hydroxyapatite and the pH of the aqueous solution is maintained at a pH of at least 4.0 during the electrodeposition step.
- 15 3. A method as claimed in claim 1 wherein the calcium phosphate compound salt is other than hydroxyapatite and the method further comprises immersing the material having the calcium phosphate compound electrodeposited thereon in an aqueous  
20 solution having a pH of not less than 4.0, whereby said the calcium phosphate compound is converted to hydroxyapatite.
- 25 4. A method as claimed in any one of the preceding claims wherein the metallic material is titanium, a titanium alloy, stainless steel or a cobalt-chromium alloy.
- 30 5. A method as claimed in any one of the preceding claims wherein the compound containing calcium ions is  $\text{Ca(OH)}_2$ ,  $\text{Ca(NO}_3)_2$ ,  $\text{CaC}_2$ ,  $\text{Ca(CH}_3\text{COO)}_2$ , calcium citrate or calcium lactate.

6. A method as claimed in any one of the preceding claims the compound containing phosphate ions is  $\text{H}_3\text{PO}_4$ ,  $\text{Na}_3\text{PO}_4$ ,  $(\text{NH}_4)_3\text{PO}_4$ ,  $\text{K}_3\text{PO}_4$  or  $(\text{NH}_4)_2\text{HPO}_4$ .

5           7. A method as claimed in any one of claims 1 to 4 wherein a compound is employed containing both calcium ions and phosphate ions which is hydroxyapatite, calcium tertiary phosphate, calcium quarternary phosphate or calcium hydrogen phosphate.

10

8. A method as claimed in any one of the preceding claims wherein the complex forming agent is citric acid, ethylenediaminetetraacetic acid (EDTA), lactic acid, or nitrilotriacetic acid (NTA).



## INTERNATIONAL SEARCH REPORT

Inter: -nal Application No

PCT/GB 97/02527

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C2509/08 A61L27/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C25D A61L A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category: Citation of document, with indication, where appropriate, of the relevant passages

Relevant to claim No.

X CHEMICAL ABSTRACTS, vol. 120, no. 10,  
7 March 1994  
Columbus, Ohio, US;  
abstract no. 116877,  
INOE, KYOSHI ET AL: "Surface treatment of  
prosthetic implants"  
XP002049280  
see abstract  
JP 05 285 212 A (ISHIFUKU METAL IND,  
JAPAN)

1,4-8

---

-/-

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"Z" document member of the same patent family

Date of the actual completion of the international search

5 December 1997

Date of mailing of the international search report

19/12/1997

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx: 31 651 apo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Van Leeuwen, R

## INTERNATIONAL SEARCH REPORT

Inter national Application No

PCT/GB 97/02527

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE WPI  Section Ch, Week 9348  Derwent Publications Ltd., London, GB;  Class D22, AN 93-382264  XP002049281  &amp; JP 05 285 212 A (ISHIFUKU METAL IND CO LTD)  see abstract  -----</p>	1,5-8
A	<p>US 5 413 693 A (REDEPENNING JODY G) 9 May 1995  see the whole document  -----</p>	2,3
A	<p>US 5 205 921 A (SHIRKANZADEH) 27 April 1993  see the whole document  -----</p>	2,3
A	<p>DE 195 04 386 A (UNIV DRESDEN TECH) 22 August 1996  see example 1  -----</p>	2,3

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 97/02527

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5413693 A	09-05-95	US 5310464 A	10-05-94
US 5205921 A	27-04-93	AU 1181092 A	07-09-92
		CA 2096850 A	05-08-92
		WO 9213984 A	20-08-92
		EP 0570417 A	24-11-93
		JP 6505052 T	09-06-94
DE 19504386 A	22-08-96	AU 4618896 A	27-08-96
		CA 2187512 A	15-08-96
		WO 9624391 A	15-08-96
		EP 0756499 A	05-02-97